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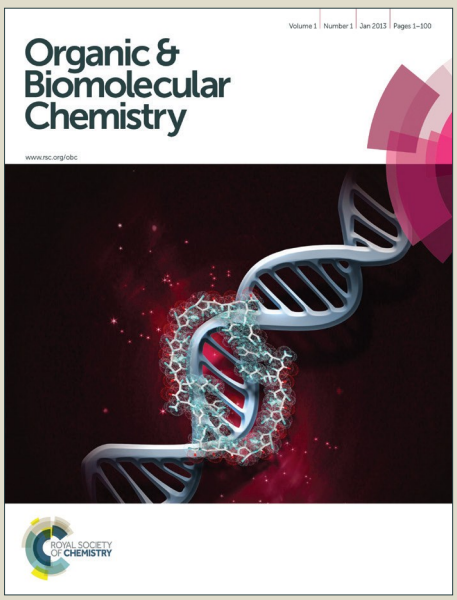

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ARTICLE

Synthesis and Orthogonal Functionalization of Oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine by Intra- and Intermolecular Pd-Catalyzed Direct C–H Bond Heteroarylation

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Laure Théveau,[a] Cédric Schneider,[a] Olivier Querolle,[b] Lieven Meerpoel,[b] Vincent Levacher [a] and Christophe Hoarau*[a]

The construction and subsequent orthogonal functionalization of a hitherto unknown oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine is reported. Palladium-catalyzed direct C–H bond functionalization methodology was used to build the tricyclic scaffold as well as to achieve the subsequent C–H bond functionalization at the C-2 position of the oxazole unit with various (hetero)aryl iodides. Remarkably, selective C–H construction and functionalization procedures preserve the chorine atom on the pyridine moiety offering a late-stage substitution site to progress in the drug design.

Introduction

Transition metal-catalyzed C–H functionalization is a step and atom economic synthetic strategy for carbon-carbon and carbon-heteroatom bonds formation which is remarkably useful for the rapid construction and decoration of highly functionalized molecules.[1] Today, this synthetic tool is actively incorporated into the synthesis of complex natural products, pharmaceuticals, agrochemicals or materials.[2] Notably several indole-containing polycyclic compounds with strong biological activities have been prepared through palladium-catalyzed direct intramolecular C–H/C–X couplings.[3] By contrast, the direct intramolecular functionalization of C–H bond methodology remains sparsely exploited to design various heteroaryl-based polycyclic nitrogen-containing heterocycles.[4] Oxazole and pyridine moieties are encountered in many biologically active natural products or naturally-occurring heterocyclic molecules, and are often used in the design of drugs.[5-8] In particular, tricyclic heteroatom- or *n*-alkyl-bridged bis-azole(one)-pyridine(piperidine) structures have been claimed in several patents to have potential biological activity to treat heart failure (**I**), psychotic disorders (**II**) or autoimmune and vascular diseases (**III**) (Figure 1).[9] On our ongoing research objective to develop palladium-catalyzed direct C–H functionalization methodologies of 1,3-diazoles for applications to medicinal and material chemistry programs,[10] a quick construction and orthogonal functionalization of original oxazole- and pyridine-based tricyclic heterocycles **IV** was undertaken (Figure 1).

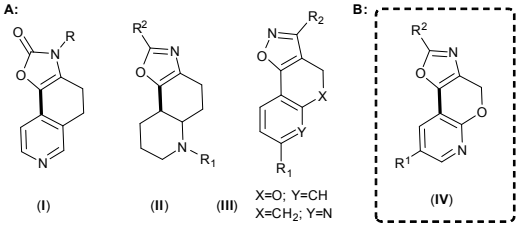

Fig. 1 (A) Reported tricyclic bis-azole(one)-pyridine(piperidine) compounds possessing biological activity. (B) Our targeted oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine analogue

The innovative two-phases construction and subsequent functionalization of the oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** is depicted in figure 2. The neat construction of the etheryl-bridged oxazolopyridine **2** involved a nucleophilic aromatic substitution S_NAr between the readily available 3-bromo-2,5-dichloropyridine (**3**) and 4-hydroxymethyloxazole (**4**), followed by an intramolecular direct C–H pyridinylation of the oxazole ring (Figure 2-A). This new polycyclic heteroaryl ether **1** was then studied in the challenging and selective intermolecular palladium-catalyzed direct C–H bond (hetero)arylation at the C-2 with various (hetero)aryl iodides, while preserving the chorine atom at the C-8 position. Finally, the chlorinated frameworks obtained were engaged as electrophiles in late-stage standard cross-couplings reactions (figure 2-B).

[a] Normandie University, COBRA, UMR 6014 et FR 3038 University Rouen; INSA Rouen; CNRS, IRCOF 1 rue Tesnière 76821 Mont Saint Aignan Cedex.
[b] Janssen Research & Development, Division of Janssen-Cilag S. A. Campus de Maigremont, BP615 27106 Val de Reuil Cedex, France.
[c] Email: christophe.hoarau@insa-rouen.fr

† Electronic Supplementary Information (ESI) available: ^{1}H NMR and ^{13}C NMR for all new compounds as well as the crystallographic data. See DOI: 10.1039/x0xx00000x

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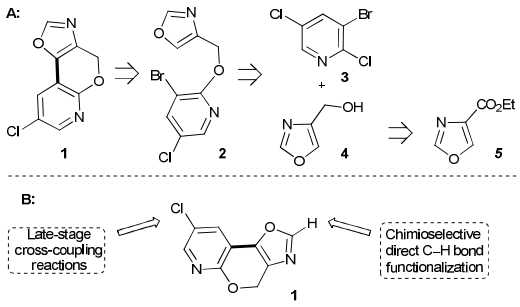
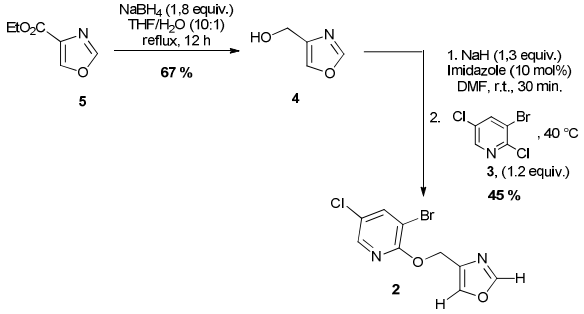


Fig. 2. (A) Retrosynthetic pathway for the construction of the platform **1**. (B) Subsequent orthogonal functionalization of the platform **1**

Results and discussion

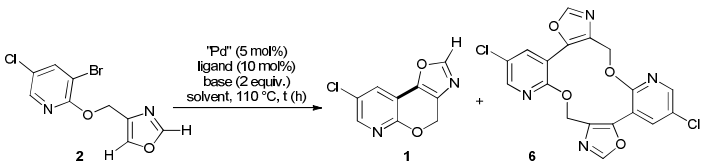
The synthesis of the etheryl-bridged oxazolopyridine **2**, as the key-intermediate towards the synthesis of oxazolopyranopyridine **1**, was firstly investigated. The first step consisted in the formation of the 4-methylhydroxyoxazole **4** which was obtained by the reduction of the readily available ethyl oxazole-4-carboxylate **5** (Scheme 1).[11] The alcohol **4** was then deprotonated by treatment with NaH in DMF and the corresponding alcoolate was engaged with the commercially available 3-bromo-2,5-dichloropyridine **3** at 40 °C. The selective S_NAr at the C-2 position of the pyridine moiety gave the expected etheryl-bridged oxazolopyridine **2** in 45% yield (Scheme 1).[12] This latter has been then used as building block for the cyclization which proceed through a selective intramolecular Pd-catalyzed direct C_5–H heteroarylation (Table 1).



Scheme 1. Synthesis of the etheryl-bridged oxazolopyridine **2**

Inspired by our previous studies on the selective concerted metallation-deprotonation (CMD)-based direct C–H arylation of alkyl-oxa(thia)-4-carboxylate with halides at the C-5 position,[10e] we initiated our investigation by a set of experiments using the $Pd(OAc)_2$ / PCy_3•HBF_4 combination as catalyst, with K_2CO_3 as base and pivalic acid as additive in 1,4-dioxane or DMF (Table 1, Entries 1-4). Although a first promising result was obtained in DMF (Table 1, entry 4), we found that the use of DMAc as solvent dramatically improved the yields (Table 1, Entry 5). This observation is in perfect accordance with previous reports that employ specifically DMAc to achieve the selective CMD-based direct C–H arylation of non-activated oxazole at the C-5 position.[13]

Table 1. Optimization of reaction parameters



Entry[a]	[Pd] source	Solvent	Base	Yield[b] (%)	Ratio **1**:**6**
1[c]	$Pd(OAc)_2$/PCy_3•HBF_4	1,4-Dioxane	K_2CO_3	10	8:2
2	$Pd(OAc)_2$/PCy_3•HBF_4	1,4-Dioxane	K_2CO_3	7	8:2
3[c]	$Pd(OAc)_2$/PCy_3•HBF_4	DMF	K_2CO_3	13	8:2
4	$Pd(OAc)_2$/PCy_3•HBF_4	DMF	K_2CO_3	20	8:2
5	$Pd(OAc)_2$/PCy_3•HBF_4	DMAc	K_2CO_3	38	8:2
6	$PdCl_2(PPh_3)_2$	DMAc	K_2CO_3	45	8:2
7	$PdCl_2(PPh_3)_2$	DMAc	$n$$Bu_4$OAc	36	8:2
8	$PdCl_2(PPh_3)_2$	DMAc	KOAc	62	8:2
9	$PdCl_2$(dppf)•CH_2Cl_2	DMAc	KOAc	65	8:2
10[d]	$PdCl_2$(dppf)•CH_2Cl_2	DMAc	KOAc	75	9:1
11[e]	*$PdCl_2$(dppf)•CH_2Cl_2*	*DMAc*	*KOAc*	*80, 72*[f]	*100*

[a]Reaction conditions: **2** (0.2 mmol), [Pd] (5 mol%), ligand (10 mol%), base (2.0 equiv), anhydrous solvent (1.5 mL). [b]Yield based on isolated product after flash chromatography. [c]PivOH (30 mol%). [d]DMAc (2 mL). [e]DMAc (4 mL). [f]Carried out on 2.76 mmol of **2**

After a screening of palladium sources and bases, the best result was obtained using Pd(dppf)•CH_2Cl_2 (5 mol%) and KOAc, base frequently used to promote the direct 5-arylation of azoles (Table 1, entries 5-9).[14] In contrast to the result reported recently by Bellina and coworker, a low efficiency was observed with nBu_4NOAc.[15] It is noteworthy that the reaction was completed in only 1 hour at 110 °C and we observed that the decrease of the temperature affect dramatically the efficiency of the reaction.[16] We noticed also the formation of a dimer **6** resulting of a homocoupling product **2** with a ratio 8:2 respectively. At this stage, the major challenge to improve the yield was to circumvent this side homocoupling reaction revealing thus the good reactivity of oxazole unit in base-assisted palladium-catalyzed direct C–H arylation with halides. In order to overcome this intermolecular side product, we found that lowering the concentration from 0.13 to 0.05 M was crucial (Table 1, entries 9-11). Interestingly, the optimized protocol was also easily scaled up from 0.2 to 2.76 mmol without a tremendous decrease of yield (Table 1 entries 11). Finally, the structure **1** and **6** were confirmed by single crystal X-ray structure determination (Figure 3).[17]

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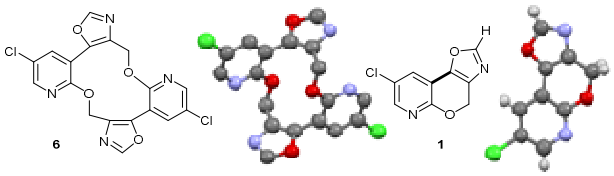
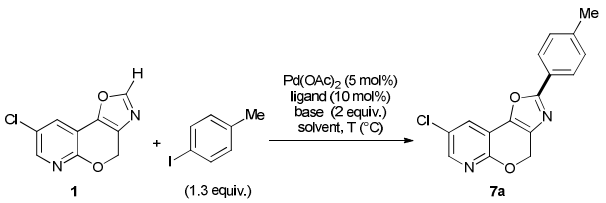


Fig. 3. X-ray single crystal structure of **1** and **6**. Only one molecule from each unit cell is shown and hydrogens are omitted for clarity

With the compound **1** in hands, a further challenging and chemo-selective direct C–H arylation was achieved with various (hetero)aryl iodides indirectly used as competitive coupling partners to the chlorinated pyridinic moiety **1** (Table 2). Regarding the highly acidic C–H bond at the C-2 position of the oxazolic moiety, we naturally employed our previously reported conditions for the palladium-catalyzed Cs_2CO_3-assisted direct C_2–H arylation of activated oxazole.[10] We were pleased to observe that by using the $Pd(OAc)_2$ / CyJohnPhos combination with 4-iodotoluene and Cs_2CO_3 in 1,4-dioxane, the expected product **7a** was obtained in fair 32% yield (Table 2, entry 1). Switching solvent to DMAc led to the formation of the arylated product **7a** in 57% yield (Table 2, entry 2).

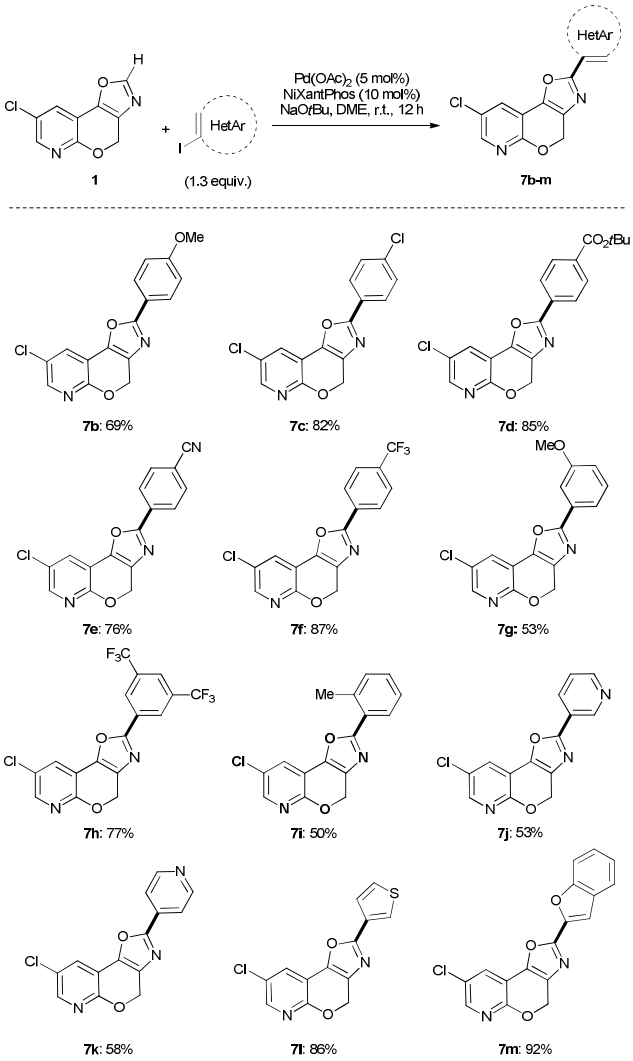
Table 2. Pd-catalyzed intermolecular direct C–H arylation under various reaction conditions



Entry	Ligand	Solvent	Base	T (°C)	t (h)	Yield (%)[a]
1	Cy-JohnPhos	1,4-dioxane	Cs_2CO_3	110	5	32
2	Cy-JohnPhos	DMAc	Cs_2CO_3	110	2	57
3	Cy-JohnPhos	DMAc	CsOAc	110	3	64
4	Cy-JohnPhos	DMAc	KOAc	110	3	40
5	Cy-JohnPhos	DMAc	*t*-BuOLi	110	2	10
6	Cy-JohnPhos	THF	*t*-BuONa	60	2	18
7	NiXantPhos	THF	*t*-BuONa	60	2	82
8	NiXantPhos	THF	*t*-BuONa	*r.t.*	12	71
9	*NiXantPhos*	*DME*	*t-BuONa*	*r.t.*	*12*	*87*
10[c]	NiXantPhos	DME	*t-BuONa*	r.t.	12	n.r.
11[c]	NiXantPhos	DME	*t-BuONa*	100	12	42

[a]Yield based on isolated product after flash chromatography. [b]With 0.2 equivalent of CuBr. [c]With 1.3 equivalents 4-bromotoluene.

Because the role of base is crucial to the metalation-deprotonation process (Table 2, entries 2-5), a screening was achieved and the best result in DMAc at 110 °C was obtained using CsOAc as base. However, we never exceeded 64% yields due to the degradation of the starting materials (**1**). To circumvent this drawback, we decided to decrease the temperature. Moreover, based on the recent work of Walsh and coworkers, we examined the efficiency of the van Leeuwen's Nixantphos as ligand (Table 2, Entries 6-7).[18] Surprisingly, the nature of the base (*t*BuONa, *t*BuOLi and *t*BuOK) as well as the ligand had crucial impact on the yield in THF at 60°C.[16] The essay dropped to 71% yield when the temperature was reduced to room temperature (Entry 8). We then screened several solvents at rt and obtained 87% yield when the reaction was conducted in DME with *t*BuONa as base (Entries 8-9).[16] Under these conditions, the reaction time to completion required 12 hours and only (hetero)aryl iodide partners work (Entries 10-11). Thus, the optimized conditions for the direct chemoselective arylation are $Pd(OAc)_2$ (5 mol%), NiXantphos (10 mol%) with *t*BuONa in DME at room temperature.



Scheme 2. Scope of the intermolecular direct C–H arylation with various (hetero)aryl iodides

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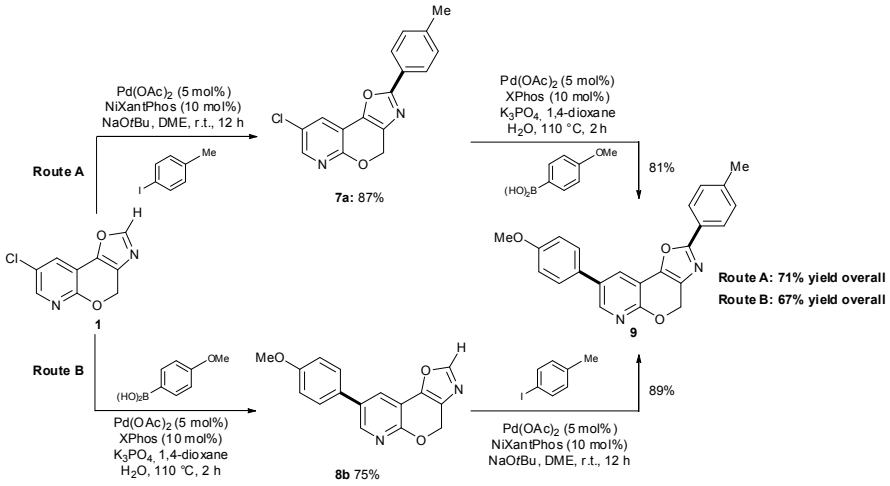
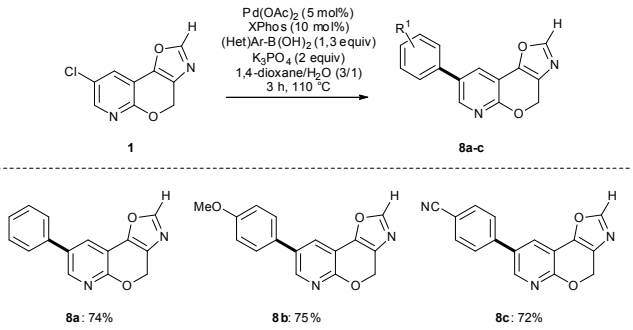


Scheme 4. Chemoselective orthogonal functionalization by C–H arylation / Suzuki-Miyaura coupling of 1

With the optimized conditions in hands, the establishment of the scope of the direct C–H arylation at the C-2 position was undertaken with a broad panel of (hetero)aryl iodides. Chemoselective direct C–H arylations of **1** were successfully achieved with aryl iodides bearing electron-withdrawing as well as electron-donating substituents affording desired 2-arylated oxazolopyranopyridines **7b-7i** in fair to excellent yields (50-87%). Importantly, these conditions proved to be compatible with the presence of important functional groups on the aromatic moiety such as ester (85%), cyano (76%) and chloro (82%). Moreover, the steric hindrance on aryl iodides has no influence on the success of the direct C–H arylation. More challenging, we then examined a series of heteroaromatic coupling partners with **1**. The reactions proceeded well with heteroaryl iodides such as 3- and 4-iodopyridines, 3-iodothiophene and 2-iodobenzofuran to afford products **7j-7m** in 53-92% yields.



Scheme 3. Suzuki-Miyaura coupling at the chlorine moiety of compound **1**

Having defined reasonable generality for the intermolecular direct C–H (hetero)arylation of oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** methodology for the synthesis of C-2 (hetero)arylated product **7**, we sought to investigate the combination of both the C–H (hetero)arylation and standard cross-coupling reaction in order to design innovative, modular and short route for the synthesis of the bis-arylated polycyclic **9** (Scheme 4). For this purpose, we next turn our attention to the chemoselective orthogonal functionalization of the 3-chloropyridine moiety **1** *via* Suzuki-Miyaura reaction.[19] After screening of several parameters (solvent, base, ligand),[16] cross-coupling reactions with aryl boronic acids bearing electron-donating and -withdrawing groups could be selectively achieved in good yields (72-75%), using XPhos as ligand and K_3PO_4 as base in 1,4-dioxane/H_2O mixture at 110 °C (Scheme 3).

As application herein, we decided to take advantage of selective direct arylation methodologies of C_2–H and C_8-Cl bonds in order to orthogonally functionalize both positions, enabling the synthesis of decorated compound **9**. The 2,8-bis-arylated product **9** could be selectively, rapidly and efficiently prepared in two routes, A and B, involving the two-step sequential combination of direct C_2–H bond arylation with aryl iodides followed by Suzuki-Miyaura reaction respectively or v*ice versa* (Scheme 4). Finally, whatever the sequence, similar overall yields were obtained (67-71%).

Conclusion

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In summary, we have reported an efficient construction and subsequent orthogonal functionalization of a new tricyclic heteroaryl ether **1** through an intra- and intermolecular palladium-catalyzed direct C–H bond (hetero)arylation. Remarkably, the intermolecular heteroarylation is functional group tolerant, step-economical, and *proceeds at room temperature in moderate to good yield with a large scope of heteroaryles iodides*. Moreover, both coupling reactions, construction and functionalization, tolerate the presence of a chlorine atom on the pyridine moiety which was subsequently used to create a new disconnection through palladium-catalyzed Suzuki-Miyaura coupling, enabling thus an opening of the chemical space.

Experimental

General experimental procedures

Commercially available reagents were used throughout without further purification. Reactions were routinely carried out under an N2 atmosphere using oven or flame-dried glassware. Melting points were determined on a hot stage melting point apparatus and are uncorrected. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded using a 300 spectrometer operating at 300 MHz (^{1}H frequency, corresponding ^{13}C and ^{19}F frequencies are 75 and 282 MHz). The chemical shifts are calibrated to residual proton and carbon resonance of $CDCl_3$ (^{1}H 7.26 and ^{13}C 77.16 ppm) or DMSO (^{1}H 2.52 and ^{13}C 39.5 ppm). In the 13C NMR spectra, signals corresponding to C, CH, CH_2, or CH_3 groups are assigned from DEPT. The obtained signal multiplicities were distinguished with the common abbreviations s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), hep (heptet), sex (sextet) and the combinations thereof. IR spectra were recorded on a FT-IR intrument. Low resolution mass spectra analyses were performed with spectrometer in chemical ionisation. High Resolution Mass spectra (HRMS) were performed under ESI conditions with a micro Q-TOF detector. All reactions were monitored by thin-layer chromatography with silica gel 60 F254 pre-coated aluminium plates (0.25 mm). Flash chromatography was performed with the indicated solvents using silica gel 60 (35-70 µm mesh).

4-(((3-bromo-5-chloropyridin-2-yl)oxy)methyl)oxazole 2. To a solution of ethyl oxazole-4-carboxylate (5 g, 35 mmol, 1 equiv.) in THF (0.3 M), $NaBH_4$ (1.8 equiv.) and H_2O (1.8 equiv.) were added. The mixture was then stirred overnight at reflux. The mixture was quenched with saturated NH_4Cl aqueous solution and then extracted 3 times with CH_2Cl_2. The combined organic layers were quickly washed with saturated aqueous NaCl solution, dried over $MgSO_4$ and concentrated in vacuo. The crude product **4** was then used without further purification as colorless oil (2.3 g, 67%). Thus, to a solution of the 4-oxazolemethanol **4** (1.139 g, 11.50 mmol) in anhydrous DMF (30 mL) was added imidazole (78 mg, 1.15 mmol, 0.1 equiv) and NaH 60% in oil (598 mg, 14.95 mmol, 1.3 equiv) at 0 °C respectively. The mixture was then stirred during 30 min at room temperature and a solution of 2,5-dichloro-4-bromopyridine (3.13 g, 13.8 mmol, 1.2 equiv) in anhydrous DMF (9 mL) was added. The reaction mixture was heated overnight at 40 °C. The mixture was then quenched with saturated NH_4Cl aqueous solution and extracted with CH_2Cl_2 (3x30 mL). The organic phase was dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/PE 1:9) to afford 4-(((3-bromo-5-chloropyridin-2-yl)oxy)methyl)oxazole **2** (1.65 g, 5.69 mmol) in 50% yield as a beige solid. mp 75-76 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 1H, *J* = 2.3 Hz), 7.89 (s, 1H), 7.82 (d, 1H, *J* = 2.3 Hz), 7.76 (d, 1H, *J* = 1.0 Hz), 5.38 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9 (C), 151.4 (CH), 143.7 (CH), 141.4 (CH), 137.4 (CH), 136.2 (C), 124.5 (C), 107.4 (C), 61.3 (CH_2); IR (neat) ν_{max} 3047, 2922, 1580, 1514, 1440, 1050 cm^{-1}; MS (ESI) m/z 288 [$M+H^+$, ^{79}Br], 290 [$M+H^+$, ^{81}Br]; HMRS (ESI-TOF): calc. for $C_9H_7N_2O_2ClBr$: 288.9379; found: 288.9370.

8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 1. A sealed pressure tube with stir bar was charged with 4-(((3-Bromo-5-chloropyridin-2-yl)oxy)methyl)oxazole **2** (60 mg, 0.2 mmol, 1 equiv.), $PdCl_2(dppf)\cdot CH_2Cl_2$ (9 mg, 0.01 mmol, 5 mol %) and KOAc (40 mg, 0.4 mmol, 2 equiv). The tube was evacuated and back-filled with argon (this was repeated three additional times). Degassed anhydrous DMAc (4 mL) was added and the reaction mixture was allowed to stir at 110 °C for 1 h. The reaction mixture was filtered through a plug of celite (washed with CH_2Cl_2) and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/PE 3:7) to afford 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (33 mg, 0.159 mmol) in 80% yield as a white solid. mp 178-179 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, 1H, *J* = 2.7 Hz), 7.95 (s, 1H), 7.56 (d, 1H, *J* = 2.7 Hz), 5.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8 (C), 152.5 (CH), 145.7 (CH), 140.8 (C), 130.8 (C), 127.9 (CH), 125.5 (C), 110.8 (C), 67.2 (CH_2); IR (neat) ν_{max} 3053, 2950, 1558, 1488, 1477, 1426, 1239, 1075 cm^{-1}; MS (ESI) m/z 209 [$M+H^+$]; HMRS (ESI-TOF): calc. for $C_9H_6N_2O_2Cl$: 209.0118; found: 209.0117.

5,14-dichloro-9,18-dihydrodioxazolo[5',4':4,5;5'',4'':10,11][1,7]dioxacyclododecino[2,3-*b*:8,9-*b*']dipyridine 6. mp 264-265 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, 2H, *J* = 2.6 Hz), 7.92 (s, 2H), 7.73 (d, 2H, *J* = 2.6 Hz), 5.26 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0 (2xC), 150.4 (2xCH), 146.8 (2xCH), 144.8 (2xC), 138.5 (2xCH), 132.8 (2xC), 124.8 (2xC), 112.9 (2xC), 61.1 ($2xCH_2$); IR (neat) ν_{max} 3133, 3059, 2918, 1567, 1503, 1450, 1429, 1301, 1234, 1083, 1031, 986 cm^{-1}; MS (ESI) m/z 417 [$M+H^+$]; HMRS (ESI-TOF): calc. for $C_{18}H_{11}N_4O_4Cl_2$: 417.0157; found: 417.0152.

General procedure for the C-2 heteroarylation

A flame-dried tube filled with argon was charged with heteroaryl iodides (0.26 mmol, 1.3 equiv), 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol,

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1.0 equiv), NiXantphos (11 mg, 0.02 mmol, 10 mol%), $Pd(OAc)_2$ (2 mg, 0.01 mmol, 5 mol%), *t*BuONa (49 mg, 0.5 mmol, 2.5 equiv). The tube was sealed, evacuated and back-filled with argon (this was repeated three additional times). Freshly degassed and anhydrous DME (1 mL) was added and the reaction mixture was stirred at room temperature for 12 hours. Then, the reaction mixture was filtered through a plug of celite (washed with CH_2Cl_2) and the solvents were removed under reduced pressure. The crude product was then purified by flash column chromatography

8-chloro-2-(*p*-tolyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 7a. Compound **7a** was prepared from 4-iodotoluene (57 mg, 0.26 mmol) and 8-chloro-4H-oxazolo[5',4':4,5]pyrano[2,3-b]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (EtOAc/PE 3:7) to afford 8-chloro-2-(*p*-tolyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7a** (52 mg, 0.174 mmol) in 87% yield as a beige solid. mp 185-186 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 1H, J = 2.5 Hz), 7.95 (d, 2H, *J* = 8.0 Hz), 7.61 (d, 1H, *J* = 2.5 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 5.72 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (C), 157.7 (C), 144.8 (CH), 142.0 (C), 140.0 (C), 132.8 (C), 129.9 (2xCH), 127.1 (CH), 126.7 (2xCH), 125.4 (C), 123.8 (C), 111.2 (C), 67.3 (CH_2), 21.7 CH_3); IR (neat) ν_{max} 3046, 1610, 1555, 1488, 1432, 1352, 1238, 1197, 1010 cm^{-1}; MS (ES) m/z 299 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{16}H_{12}N_2O_2Cl$: 299.0587; found: 299.0592.

8-chloro-2-(4-methoxyphenyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 7b. Compound **7b** was prepared from 4-iodoanisole (61 mg, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (EtOAc/PE 3:7) to afford 8-chloro-2-(4-methoxyphenyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7b** (43 mg, 0.137 mmol) in 69% yield as a beige solid. mp 215-216 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, 2H, J = 8.9 Hz), 7.96 (d, 1H, J = 2.5 Hz), 7.59 (d, 1H, *J* = 2.5 Hz), 7.00 (d, 2H, *J* = 8.9 Hz), 5.71 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (C), 162.2 (C), 157.6 (C), 144.7 (CH), 139.7 (C), 132.9 (C), 128.5 (2xCH), 126.9 (CH), 125.4 (C), 119.2 (C), 114.6 (2xCH), 111.3 (C), 67.3 (CH_2), 55.6 (CH_3); IR (neat) ν_{max} 3066, 2999, 2938, 1609, 1488, 1434, 1240, 1197, 1034 cm^{-1}; MS (ESI) m/z 315 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{16}H_{12}N_2O_3Cl$: 315.0536; found: 315.0536.

8-chloro-2-(4-chlorophenyl)-4H-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 7c. Compound **7c** was prepared from 1-chloro-4-iodobenzene (62 mg, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (EtOAc/PE 15:85) to afford 8-chloro-2-(4-chlorophenyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7c** (52 mg, 0.163 mmol) in 82% yield as a white solid. mp 225-226 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 2H, *J* = 8.4 Hz), 7.97 (d, 1H, *J* = 2.5 Hz), 7.59 (d, 1H, *J* = 2.5 Hz), 7.47 (d, 2H, *J* = 8.4 Hz), 5.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9 (C), 157.7 (C), 145.3 (CH), 140.6 (C), 137.6 (C), 133.0 (C), 129.5 (2xCH), 127.9 (2xCH), 127.4 (CH), 125.5 (C), 125.0 (C), 110.9 (C), 67.2 (CH_2); IR (neat) ν_{max} 3059, 2972, 1552, 1477, 1433, 1251, 1090, 887 cm^{-1}; MS (ESI) m/z 319 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{15}H_9N_2O_2Cl_2$: 319.0041; found: 319.0044.

***tert*-butyl 4-(8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridin-2-yl)benzoate 7d.** Compound **7d** was prepared from tert-butyl 4-iodobenzoate (61 mg, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (EtOAc/PE 2:8) to afford tert-butyl 4-(8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine-2-yl)benzoate **7d** (65 mg, 0.169 mmol) in 85% yield as a yellow solid. mp 150-151 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 4H), 8.00 (d, 1H, *J* = 2.5 Hz), 7.64 (d, 1H, *J* = 2.5 Hz), 5.72 (s, 2H), 1.62 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (C), 162.9 (C), 157.7 (C), 145.3 (CH), 140.9 (C), 134.2 (C), 133.1 (C), 130.1 (2xCH), 129.6 (C), 127.5 (CH), 126.3 (2xCH), 125.5 (C), 110.8 (C), 81.8 (C), 67.1 (CH_2), 28.2 (3xCH_3); IR (neat) ν_{max} 2979, 2938, 1708, 1428, 1290, 1243, 1161, 1107 cm^{-1}; MS (ESI) m/z 385 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{20}H_{18}N_2O_4Cl$: 385.0955; found: 385.0948.

4-(8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridin-2-yl)benzonitrile 7e. Compound **7e** was prepared from 4-iodobenzonitrile (60 mg, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (CH_2Cl_2/EtOAc 97:3) to afford 4-(8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine-2-yl)benzonitrile **7e** (45 mg, 0.145 mmol) in 73% yield as a yellow solid. mp 266-267 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 2H, *J* = 8.4 Hz), 8.01 (d, 1H, *J* = 2.5 Hz), 7.78 (d, 2H, *J* = 8.4Hz), 7.63 (d, 1H, *J* = 2.5 Hz), 5.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (C), 157.9 (C), 145.9 (CH), 141.6 (C), 133.4 (C), 132.9(2xCH), 130.2 (C), 127.8 (CH), 127.0 (2xCH), 125.7 (C), 118.2 (C), 114.5 (C), 110.6 (C), 67.0 (CH_2); IR (neat) ν_{max} 3069, 2227, 1551, 1464, 1428, 1243 cm^{-1}; MS (ESI) m/z 310 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{16}H_9N_3O_2Cl$: 310.0383; found: 310.0372.

8-chloro-2-(4-(trifluoromethyl)phenyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 7f. Compound **7f** was prepared from 4-iodobenzotrifluoride (71 mg, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (EtOAc/PE 2:8) to afford 8-chloro-2-(4-(trifluoromethyl)phenyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7f** (61 mg, 0.173 mmol) in 87% yield as a yellow solid. mp 180-181 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, 2H, *J* = 8.2 Hz), 8.00 (d, 1H, *J* = 2.6 Hz), 7.75 (d, 2H, *J* =

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8.2 Hz), 7.64 (d, 1H, *J* = 2.6 Hz), 5.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2 (C), 157.7 (C), 145.5 (CH), 141.1 (C), 133.0 (C), 132.3 (C, *J* = 33 Hz), 129.5 (C), 127.5 (CH), 126.8 (2xCH), 126.1 (2xCH, *J* = 3.3 Hz), 125.5 (C), 123.7 (C, *J* = 275 Hz), 110.6 (C), 67.0 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.9; IR (neat) ν_{max} 3065, 1619, 1555, 1468, 1435, 1320, 1167, 1108 cm^{-1}; MS (ESI) m/z 354 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{16}H_9N_2O_2ClF_3$: 353.0304; found: 353.0308.

8-chloro-2-(3-methoxyphenyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 7g. Compound **7g** was prepared from 3-iodoanisole (61 mg, 32 µL, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (EtOAc/PE 4:6) to afford 8-chloro-2-(3-methoxyphenyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7g** (33 mg, 0.105 mmol) in 53% yield as a yellow solid. mp 199-200 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 1H, *J* = 2.5 Hz), 7.65 (d, 1H, *J* = 7.7 Hz), 7.61 (d, 1H, *J* = 2.5 Hz), 7.57-7.56 (m, 1H), 7.40 (t, 1H, *J* = 8.1 Hz), 7.05 (dd, 1H, *J* = 2.5 and 8.1 Hz), 5.71 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (C), 160.1 (C), 157.7 (C), 145.1 (CH), 140.4 (C), 132.9 (C), 130.3 (CH), 127.7 (C), 127.3 (CH), 125.5 (C), 119.1 (CH), 117.9 (CH), 111.2 (CH), 111.1 (C), 67.2 (CH_2), 55.6 (CH_3); IR (neat) ν_{max} 3066, 2999, 2923, 1599, 1469, 1432, 1224, 1030 cm^{-1}; MS (ESI) m/z 315 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{16}H_{12}N_2O_3Cl$: 315.0536; found: 315.0538.

2-(3,5-bis(trifluoromethyl)phenyl)-8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 7h. Compound **7h** was prepared from 1-iodo-3,5-trifluoromethylbenzene (84 mg, 47 µL, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (CH_2Cl_2) to afford 2-(3,5-bis(trifluoromethyl)phenyl)-8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7h** (65 mg, 0.155 mmol) in 77% yield as a beige solid. mp 187-188 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (bs, 2H), 8.04 (d, 1H, *J* = 2.5 Hz), 7.99 (bs, 1H), 7.72 (d, 1H, *J* = 2.5 Hz), 5.74 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7 (C), 157.9 (C), 146.1 (CH), 141.8 (C), 133.4 (C, *J* = 34 Hz), 133.2 (C), 132.5 (C, *J* = 34 Hz), 128.4 (C), 128.0 (CH), 126.4 (2xCH, *J* = 3.7 Hz), 125.7 (C), 126.6 (C, *J* = 271 Hz), 124.4 (CH, *J* = 3.7 Hz), 119.3 (C, *J* = 271 Hz), 110.4 (C), 66.9 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ 63.1; IR (neat) ν_{max} 3086, 3059, 2923, 1470, 1436, 1374, 1301, 1272, 1125 cm^{-1}; MS (ESI) m/z 421 [M+H$^+$]. HMRS (ESI-TOF): calc. for $C_{17}H_8N_2O_2ClF_6$: 421.0178; found: 421.0173.

8-chloro-2-(*o*-tolyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 7i. Compound **7i** was prepared from 2-iodotoluene (57 mg, 34 µL, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (EtOAc/PE 2:8) to afford 8-chloro-2-(*o*-tolyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7i** (34 mg, 0.114 mmol) in 57% yield as a yellow solid. mp 137-139 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, 1H, *J* = 1.6 and 9.0 Hz), 7.97 (d, 1H, *J* = 2.5 Hz), 7.58 (d, 1H, *J* = 2.5 Hz), 7.41-7.32 (m, 3H), 5.74 (s, 2H), 2.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2 (C), 157.8 (C), 144.9 (CH), 139.8 (C), 138.0 (C), 132.7 (C), 132.0 (CH), 130.9 (CH), 129.0 (CH), 127.3 (CH), 126.3 (CH), 125.5 (C), 125.4 (C), 111.2 (C), 67.4 (CH_2), 22.3 (CH_3); IR (neat) ν_{max} 3073, 2924, 1673, 1601, 1550, 1454, 1429, 1238, 1200, 1048 cm^{-1}; MS (ESI) m/z 299 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{16}H_{12}N_2O_2Cl$: 299.0587; found: 299.0582.

8-chloro-2-(pyridin-3-yl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 7j. Compound **7j** was prepared from 3-iodopyridine (54 mg, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (EtOAc/PE 7:3) to afford 8-chloro-2-(pyridin-3-yl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7j** (30 mg, 0.105 mmol) in 53% yield as a yellow solid. mp 235-236 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (bs, 1H), 7.74 (d, 1H, *J* = 3.7 Hz), 8.32 (t, 1H, *J* = 1.8 and 8.0 Hz), 8.01 (d, 1H, *J* = 2.5 Hz), 7.64 (d, 1H, *J* = 2.5 Hz), 7.45 (dd, 1H, *J* = 4.9 and 8.0 Hz), 5.73 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4 (C), 157.8 (C), 151.9 (CH), 147.9 (CH), 145.6 (CH), 141.1 (C), 133.7 (CH), 133.0 (C), 127.7 (CH), 125.6 (C), 123.9 (CH), 122.9 (C), 110.7 (C), 67.1 (CH_2); IR (neat) ν_{max} 3068, 2922, 1553, 1464, 1427, 1243, 1004 cm^{-1}; MS (ESI) m/z 286 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{14}H_9N_3O_2Cl$: 286.0383; found: 286.0387.

8-chloro-2-(pyridin-4-yl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 7k. Compound **7k** was prepared from 4-iodopyridine (54 mg, 50 µL, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (EtOAc/PE 8:2) to afford 8-chloro-2-(pyridin-4-yl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7k** (33 mg, 0.116 mmol) in 58% yield as a yellow solid. mp 197-198 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, 2H, *J* = 6.0 Hz), 8.03 (d, 1H, *J* = 2.5 Hz), 7.89 (d, 2H, *J* = 6.0 Hz), 7.66 (d, 1H, *J* = 2.5 Hz), 5.73 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (C), 157.9 (C), 150.9 (2xCH), 146.0 (CH), 141.7 (C), 133.4 (C), 133.2 (C), 127.9 (CH), 125.7 (C), 120.0 (2xCH), 110.5 (C), 67.0 (CH_2); IR (neat) ν_{max} 3065, 1619, 1555, 1468, 1435, 1238, 1010 cm^{-1}; MS (ESI) m/z 286 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{14}H_9N_3O_2Cl$: 286.0383; found: 286.0378.

8-chloro-2-(thiophen-3-yl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 7l. Compound **7l** was prepared from 2-iodothiophene[19] (55 mg, 27 µL, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (EtOAc/PE 3:7) to afford 8-chloro-2-(thiophen-3-yl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7l** (50 mg, 0.172 mmol)

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in 86% yield as a yellow solid. mp 190-191 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, 1H, *J* = 1.2 and 3.0 Hz), 7.96 (d, 1H, *J* = 2.5 Hz), 7.62 (dd, 1H, *J* = 1.2 and 5.1 Hz), 7.58 (d, 1H, *J* = 2.5 Hz), 7.43 (dd, 1H, *J* = 3.0 and 5.1 Hz), 5.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6 (C), 157.7 (C), 144.9 (CH), 139.7 (C), 132.6 (C), 128.5 (C), 127.4 (CH), 127.1 (CH), 126.9 (CH), 125.9 (CH), 125.4 (C), 111.1 (C), 67.2 (CH_2); IR (neat) ν_{max} 3080, 2925, 1481, 1584, 1432, 1246, 1036, 869 cm^{-1}; MS (ESI) m/z 291 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{13}H_8N_2O_2SCl$: 290.9995; found: 290.9989.

8-chloro-2-(benzofuran-2-yl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 7m. Compound **7m** was prepared from 2-iodobenzofuran[20] (64 mg, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **A**. The crude product was purified by flash column chromatography (EtOAc/PE 3:7) to afford 8-chloro-2-(benzofuran-2-yl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7m** (60 mg, 0.185 mmol) in 93% yield as a yellow solid. mp 227-229 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, 1H, J = 2.5 Hz), 7.68 (d, 1H, *J* = 7.8 Hz), 7.64 (d, 1H, *J* = 2.5 Hz), 7.59 (d, 1H, *J* = 8.3 Hz), 7.45 (s, 1H), 7.41 (dd, 1H, *J* = 1.0 and 7.4 Hz), 7.32 (t, 1H, , *J* = 7.4 Hz), 5.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7 (C), 156.1 (C), 155.6 (C), 145.6 (CH), 142.9 (C), 140.8 (C), 132.9 (C), 127.6 (CH), 127.5 (C), 127.1 (CH), 125.6 (C), 124.1 (CH), 122.3 (CH), 112.0 (CH), 110.6 (C), 109.1 (CH), 67.0 (CH_2); IR (neat) ν_{max}: 3053, 2923, 1622, 1549, 1468, 1429, 1246, 1002 cm^{-1}; MS (ESI) m/z 325 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{17}H_{10}N_2O_3Cl$: 325.0380; found: 325.0382.

General procedure for the Suzuki-Miyaura cros-coupling

A flame-dried tube filled with argon was charged with boronic acid (0.26 mmol, 1.3 equiv), 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv), XPhos (10 mg, 0.02 mmol, 10 mol%), $Pd(OAc)_2$ (3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (85 mg, 0.4 mmol, 2.0 equiv). The tube was sealed, evacuated and back-filled with argon (this was repeated three additional times). Freshly degassed 1,4-dioxane (600 µL) as well as H_2O (200 µL) were added and the reaction mixture was stirred at 110 °C for 4 hours. Then, the reaction mixture was filtered through a plug of celite (washed with CH_2Cl_2) and the solvents were removed under reduced pressure. The crude product was then purified by flash column chromatography.

8-phenyl-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 8a. Compound **8a** was prepared from phenylboronic acid (32 mg, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **B**. The crude product was purified by flash column chromatography (EtOAc/PE 4:5) to afford 8-phenyl-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **8a** (35 mg, 0.140 mmol) in 70% yield as a beige solid. mp 144-146 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, 1H, *J* = 2.4 Hz), 7.93 (s, 1H), 7.77 (d, 1H, *J* = 2.4 Hz), 7.54-7.51 (m, 2H), 7.47-7.42 (m, 2H), 7.39-7.34 (m, 1H), 5.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9 (C), 152.0 (CH), 145.6 (CH), 141.6 (C), 136.9 (C), 131.5 (C), 129.9 (C), 129.1 (2xCH), 127.9 (CH), 126.6 (3xCH), 109.7 (C), 67.0 (CH_2); IR (neat) ν_{max} 3091, 2926, 1647, 1601, 1439 cm^{-1}; MS (ESI) m/z 251 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{15}H_{11}N_2O_2$: 251.0821; found: 251.0815.

8-(4-methoxyphenyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 8b. Compound **8b** was prepared from 4-methoxyphenylboronic acid (40 mg, 0.26 mmol, 1.3 equiv) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **B**. The crude product was purified by flash column chromatography (EtOAc/PE 1:1) to afford 8-(4-methoxyphenyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **8b** (42 mg, 0.150 mmol) in 75% yield as a beige solid. mp 201-202 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.94 (s, 1H), 7.74 (s, 1H), 7.46 (d, 2H, *J* = 8.3 Hz), 6.98 (d, 2H, *J* = 8.3 Hz), 5.68 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6 (C), 158.5 (C), 152.0 (CH), 145.2 (CH), 141.8 (C), 131.3 (C), 129.9 (C), 129.4 (C), 127.8 (2xCH), 126.3 (CH), 114.6 (2xCH), 109.6 (C), 66.9 (CH_2), 55.5 (CH_3); IR (neat) ν_{max} 3142, 2926, 1557, 1481, 1463, 1438, 1251, 1236, 1198, 1016, 1006 cm^{-1}; MS (ESI) m/z 281 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{16}H_{13}N_2O_3$: 281.0926; found: 281.0919.

8-(4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridin-8-yl)benzonitrile 8c. Compound **8c** was prepared from 4-cyanophenylboronic acid (39 mg, 0.26 mmol) and 8-chloro-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **1** (42 mg, 0.2 mmol, 1.0 equiv) according to the general procedure **B**. The crude product was purified by flash column chromatography ($EtOAc/CH_2Cl_2$ 2:8) to afford 8-(4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridin-8-yl)benzonitrile **8c** (35 mg, 0.140 mmol) in 68% yield as a beige solid. mp 241-242 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, 1H, *J* = 2.3 Hz), 7.98 (s, 1H),7.80 (d, 1H, *J* = 2.3 Hz), 7.75 (d, 2H, *J* = 8.4 Hz), 7.66 (d, 2H, *J* = 8.4 Hz), 5.74 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159. 8 (C), 152.4 (CH), 145.8 (CH), 141.5 (C), 141.2 (C), 133.0 (2xCH), 130.3 (C), 129.6 (C), 127.3 (2xCH), 126.5 (CH), 118.6 (C), 111.7 (C), 110.1 (C), 67.3 (CH_2); IR (neat) ν_{max} 3053, 2925, 2223, 1607, 1575, 1489, 1445, 1063 cm^{-1}; MS (ESI) m/z 276 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{16}H_{10}N_3O_2$: 276.0773; found: 276.0771.

8-(4-methoxyphenyl)-2-(*p*-tolyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine 9.

Route A, procedure (7a → 9): A flame-dried tube filled with argon was charged with 4-methoxyphenyl boronic acid (46 mg, 0.304 mmol, 1.3 equiv), 8-chloro-2-(*p*-tolyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **7a** (70 mg, 0.234 mmol, 1.0 equiv), XPhos (12 mg, 0.023 mmol, 10 mol%), $Pd(OAc)_2$ (3 mg, 0.012 mmol, 5 mol%), K_3PO_4 (105 mg, 0.492 mmol, 2.0 equiv). The tube was sealed, evacuated and back-filled with argon (this was repeated three additional times). Freshly degassed 1,4-dioxane (600 µL) as well as H_2O (200 µL) were added and the reaction mixture was stirred at 110 °C for

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4 hours. Then, the reaction mixture was filtered through a plug of celite (washed with CH_2Cl_2) and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/PE 4:6) to afford 8-(4-methoxyphenyl)-2-(*p*-tolyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **9** (70 mg, 0.174 mmol) in 81% yield as a yellow solid.

Route B, procedure (8b → 9): A flame-dried tube filled with argon was charged with heteroaryl iodides (51 mg, 0.232 mmol, 1.3 equiv), 8-(4-methoxyphenyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **8b** (50 mg, 0.178 mmol, 1.0 equiv), NiXantphos (10 mg, 0.018 mmol, 10 mol%), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 5 mol%), NaO*t*Bu (39 mg, 0.5 mmol, 2.5 equiv). The tube was sealed, evacuated and back-filled with argon (this was repeated three additional times). Freshly degassed and anhydrous DME (900 µL) was added and the reaction mixture was stirred at room temperature for 12 hours. Then, the reaction mixture was filtered through a plug of celite (washed with CH_2Cl_2) and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/PE 4:6) to afford 8-(4-methoxyphenyl)-2-(*p*-tolyl)-4*H*-oxazolo[5',4':4,5]pyrano[2,3-*b*]pyridine **9** (59 mg, 0.159 mmol) in 89% yield as a yellow solid. mp 207-209 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, 1H, J = 2.4 Hz), 7.97 (d, 2H, J = 8.2 Hz), 7.78 (d, 1H, J = 2.4 Hz), 7.51 (d, 2H, J = 8.7 Hz), 7.29 (d, 2H, J = 8.2 Hz), 7.00 (d, 2H, J = 8.7 Hz), 5.72 (s, 2H), 3.86 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (C), 159.6 (C), 158.4 (C), 144.5 (CH), 141.6 (C), 141.0 (C), 132.0 (C), 131.2 (C), 129.8 (2xCH), 129.6 (C), 127.8 (2xCH), 126.5 (2xCH), 125.7 (CH), 124.1 (C), 114.6 (2xCH), 110.0 (C), 67.1 (CH_2), 55.5 (CH_3), 21.7 (CH_3); IR (neat) ν_{max} 3039, 2932, 1609, 1489, 1467, 1439, 1203, 1244 cm^{-1}; MS (ESI) *m/z* 371 [M+H$^+$]; HMRS (ESI-TOF): calc. for $C_{23}H_{19}N_2O_3$: 371.1398; found: 371.1385.

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